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<p>(54) Title: <b>METHODS AND COMPOSITIONS FOR LOWERING INTRAOCULAR PRESSURE</b></p> <p>(57) Abstract</p> <p>Quinine compounds are incorporated into ophthalmically acceptable carriers for administration to the eye in order to lower intraocular pressure. Such formulations are particularly suitable for treating glaucoma and/or other disorders related to elevated intraocular pressure.</p>		

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METHODS AND COMPOSITIONS FOR  
LOWERING INTRAOCULAR PRESSURE

BACKGROUND OF THE INVENTION

1. Field of the Invention

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The present invention relates generally to compositions and methods for lowering intraocular pressure and more particularly to the administration of quinine and quinidine, and ATP-sensitive K<sup>+</sup> channel inhibitors to the eye to lower intraocular pressure for the treatment of glaucoma.

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Glaucoma is an ocular disorder that is often manifested as an elevated intraocular pressure, i.e., pressure in the anterior chamber of the eye. It is presently believed that such elevated pressure results from inadequate transport of the intraocular fluid from the anterior chamber, resulting in a detrimental pressure increase. If left untreated, glaucoma will eventually lead to loss of vision in the affected eye. Current treatment methods include forming small laser penetrations in the eye to release excess pressure, as well as the use of systemic and topical drugs for lowering intraocular pressure. Of particular interest to the present invention, topically applied drugs for the treatment of glaucoma include pilocarpine, a cholinergic; timolol maleate, a  $\beta$ -adrenergic receptor blocking agent; epinephrine, an  $\alpha$ - and  $\beta$ -adrenergic receptor agonist; dipivefrin, a pro drug of epinephrine; and demecarium bromide, a cholinesterase inhibitor. While these drugs are generally effective, they can have significant adverse side effects, even when administered topically. Topical administration to the eye results in significant absorption leading to such undesirable systemic effects.

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Therefore it would be desirable to provide additional drugs useful for the treatment of glaucoma and other disorders related to elevated intraocular pressure, particularly where such drugs have fewer or reduced side effects when compared to present drugs when topically applied. Such drugs should be safe, relatively non-toxic, and be amenable to incorporation in

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carriers and vehicles suitable for administration to the eye, either topically, by injection, or by ocular insert. These and other objectives will be met by the methods and compositions of the present invention, as described in more detail hereinafter.

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#### SUMMARY OF THE INVENTION

Novel methods and compositions for lowering intraocular pressure in the eye of a patient have been discovered. The compositions may comprise at least one quinine compound present in a non-phosphate ophthalmically acceptable carrier in an amount effective to lower intraocular pressure when administered to an eye having elevated intraocular pressure. The quinine compounds are preferably quinine, quinidine, and therapeutically equivalent salts and derivatives thereof, and are preferably present in the compositions in concentrations from about 0.1% to 5% by weight. Particular formulations include those suitable for topical application, for injection, and for combination in an ocular insert. Alternatively, the compositions may comprise at least one ATP-sensitive  $K^+$  channel inhibiting compound present in an ophthalmically acceptable carrier in an amount effective to lower intraocular pressure when administered to an eye having elevated intraocular pressure. The ATP-sensitive  $K^+$  channel inhibiting compounds are preferably sulfonylurea compounds, more preferably being selected from the group consisting of glybenclamide, glipizide, tolbutamide, and tolazamide, and are preferably present in the compositions in concentrations from about 0.1% to 5% by weight. Particular formulations include those suitable for topical application, for injection, and for combination in an ocular insert.

Methods according to the present invention comprise administering such compositions directly to the eye in an amount effective to lower the intraocular pressure. Suitable administration methods include topical application, injection, and timed release using an ocular insert or equivalent formulation.

In a first aspect, the methods and compositions of the present invention are particularly useful for the treatment of glaucoma, and overcome many of the limitations of prior glaucoma treatment methods and compositions.

#### DESCRIPTION OF SPECIFIC EMBODIMENTS

In a first aspect, the methods and compositions of the present invention are intended for treatment of glaucoma and other conditions which manifest elevated intraocular pressure in the eye of a patient, particularly human patients, but including other mammalian hosts. Glaucoma is a term which embraces a group of ocular diseases characterized by elevated intraocular pressure levels which can damage the eye. Elevated intraocular pressures often exceed 20 mm/Hg and it is desirable that such elevated pressures be lowered to below 18 mm/Hg. In the case of low-tension glaucoma, it is desirable that the intraocular pressure be lowered below that exhibited by the patient prior to treatment. Glaucoma diseases are well-described in the medical literature. See, e.g., Leibowitz et al. (1980) *Surv. Ophthalmol.* 24 (Suppl.):366-400 and Leske (1983) *Am. J. Epidemiol.* 118:166-191. Other conditions which result in elevated intraocular pressure levels include cataract surgery, steroid treatment, and treatment with other drugs known to cause intraocular pressure. The methods and compositions of the present invention are intended to treat all such conditions, preferably in order to lower the intraocular pressure to a manageable level as described above. Intraocular pressure can be measured by conventional tonometry techniques. A particularly convenient method for measuring intraocular pressure is the use of the Tono-Pen as described in Minckler et al. (1987) *Am. J. Ophthalmol.* 104:168-173.

The methods and compositions of the present invention rely on administering quinine compounds directly to the eye of the patient or host. Quinine compounds useful for the present invention include quinine (6'-methoxycinchonan-9-ol), quinidine ( $\beta$ -quinine, an enantiomeric form of quinine), and therapeutically equivalent salts and derivatives thereof. In addition to quinine and quinidine, particularly useful salts

and derivatives include quinine sulfate, quinine acid sulfate, quinine bisulfate, quinine urea hydrochloride, quinine carbonate, quinine ethyl carbonate, quinine gluconate, quinine hydroiodide, quinine hydrobromide, quinine hydrochloride, 5 quinidine sulfate, quinidine gluconate, and quinidine polygalacturonate. Quinine and quinidine are well-known drugs, amply described in the patent and medical literature, and biologically equivalent forms of both quinine and quinidine are well-known.

10 In a second aspect, the methods and compositions of the present invention rely on administering ATP-sensitive  $K^+$  channel inhibiting compounds directly to the eye of the patient or host. Suitable ATP-sensitive  $K^+$  channel inhibiting compounds useful for the treatment of elevated intraocular 15 pressure conditions include sulfonylureas, such as glybenclamide, glipizide, tolbutamide, and tolazamide (each of these compounds is described in the Merck Index, 10th Edition, with suitable source information provided), and therapeutically equivalent salts and derivatives thereof.

20 Therapeutically equivalent salts and derivatives are those salts and derivatives of the parent compounds which retain biological activity, i.e. the ability to lower intraocular pressure, which are biologically acceptable to treated hosts, and which do not possess other properties which 25 render them unsuitable for therapeutic use. The preparation of therapeutically equivalent salts and derivatives is well known in the pharmaceutical arts, as described in convention texts such as Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania, 16th Edition, 1982.

30 The ATP-sensitive  $K^+$  channel is one of the approximately 15  $K^+$  channels that have been identified. The ATP-sensitive  $K^+$  channel is regulated by intracellular ATP such that it is spontaneously active in the absence of ATP and closed by increasing ATP concentration in the cytoplasmic side 35 of the membrane. The ATP-sensitive  $K^+$  channel is not activated by intraocular  $Ca^{+2}$ , and gating of the channel is independent of membrane potential. The channel is selective for  $K^+$ , and it is selectively inhibited by sulfonylurea compounds, such as

Topical compositions for delivering the quinine or ATP-sensitive  $K^+$  channel inhibiting compounds of the present invention will typically comprise the quinine compound present in a suitable ophthalmically acceptable carrier, including both organic and inorganic carriers. Exemplary ophthalmically acceptable carriers include water, buffered aqueous solutions, isotonic mixtures of water and water-immiscible solvents, such as alkanols, arylalkanols, vegetable oils, polyalkalene glycols, petroleum-based jellies, ethyl cellulose, ethyl oleate, carboxymethylcelluloses, polyvinylpyrrolidones, isopropyl myristates, and the like. It is important that the formulations be free from phosphates, and that only non-phosphate buffers be employed. Suitable buffers include sodium chloride, sodium borate, sodium acetate, gluconates, and the like. Phosphate buffers are not suitable because of the low solubility of quinine in the presence of phosphate ions.

The formulations of the present invention may also contain ophthalmically acceptable auxiliary components, such as emulsifiers, preservatives, wetting agents, thixotropic agents (e.g., polyethylene glycols, antimicrobials, chelating agents, and the like. Particularly suitable antimicrobial agents include quaternary ammonium compounds, benzalkonium chloride, phenylmercuric salts, thimerosal, methyl paraben, propyl paraben, benzyl alcohol, phenylethanol, sorbitan, monolaurate, triethanolamine oleate, polyoxyethylene sorbitan monopalmitate, dioctyl sodium sulfosuccinate, monothioglycerol, and the like. Ethylenediamine tetracetic acid (EDTA) is a suitable chelating agent.

The following formulations are exemplary of the compositions of this invention. These formulations are illustrative only and are not intended to limit the scope of this invention and should not be so construed.

#### FORMULA 1

A sterile solution for topically treating glaucoma or reducing intraocular pressure and which is well tolerated by the eye is prepared as follows:

	<u>Component</u>	<u>Amount</u>
	Quinine	100 $\mu$ g to 20 mg
	Sodium chloride	8 mg
	Boric acid	1 mg
5	Benzalkonium chloride	0.1 mg
	Hydrochloric acid/sodium hydroxide	pH 7.0
	Water for injection (qs)	1 ml

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## FORMULA 2

A sterile solution for topically treating glaucoma or reducing intraocular pressure is prepared as described in Formula 1 except that quinidine is used in place of quinine.

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## FORMULA 3

An injectable solution for use in treating glaucoma or reducing intraocular pressure is prepared as follows:

	<u>Component</u>	<u>Amount</u>
20	Quinine	100 $\mu$ g to 20 mg
	Methyl paraben	1 mg
	Propyl paraben	1 mg
	Sodium chloride	5 mg
	Water for injection (qs)	1 ml

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## FORMULA 4

A sterile injectable solution for treating glaucoma or decreasing intraocular pressure is prepared as described in Formula 3 except that quinidine is used in place of quinine.

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## FORMULA 5

A sterile solution for topically treating glaucoma or reducing intraocular pressure and which is well tolerated by the eye is prepared as follows:

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	<u>Component</u>	<u>Amount</u>
	Glybenclamide	100 $\mu$ g to 20 mg
	Sodium chloride	8 mg
	Boric acid	1 mg
5	Benzalkonium chloride	0.1 mg
	Hydrochloric acid/sodium hydroxide	pH 7.0
	Water for injection (qs)	1 ml

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## FORMULA 6

An injectable solution for use in treating glaucoma or reducing intraocular pressure is prepared as follows:

	<u>Component</u>	<u>Amount</u>
	Glybenclamide	100 $\mu$ g to 20 mg
15	Methyl paraben	1 mg
	Propyl paraben	1 mg
	Sodium chloride	5 mg
	Water for injection (qs)	1 ml

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The following examples are offered by way of illustration, not by way of limitation.

## EXPERIMENTAL

25 Quinine Compounds

Quinine and quinidine formulations were tested for the ability to lower intraocular pressure in normal rabbits. Formulations were prepared as solutions in sterile distilled water and administered as follows. Seventy New Zealand white rabbits were divided into four groups: 25 rabbits were treated with the vehicle; 20 were treated with timolol; 15 were treated with quinine dissolved in the vehicle (8 mg NaCl, 1.0 mg boric acid, pH 7.3, water to 1 ml); and 10 were treated with quinidine dissolved in the vehicle. Each animal received 80  $\mu$ l of solution in two doses, 40  $\mu$ l each, at an interval of two minutes. Intraocular pressure was determined with a Tono-pen before administration of the solutions ("0" time) and at one

and 2 hours following administration. The results were as set forth in Table 1.

TABLE 1

5	<u>Formulation<sup>1</sup></u>	<u>Intraocular Pressure<sup>2</sup></u>		
		<u>0 hr.</u>	<u>1 hr.</u>	<u>2 hr.</u>
	Sterile water	100	95	97
	0.1% Quinine	100	87	91
	0.5% Quinine	100	78	87
10	1.0% Quinine	100	75	89
	1.0% Quinidine	100	82	97

1. Wt. percent quinine or quinidine in NaCl/borate buffer.

15 2. Percent of initial pressure.

These results show that quinine compounds are effective to lower intraocular pressure when administered *in vivo* to the eye.

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ATP-Sensitive K<sup>+</sup>

Channel Inhibiting Compounds

Formulations of inhibitors of ATP-sensitive K<sup>+</sup> channels (Table 2) were tested for their ability to decrease intraocular pressure in normal rabbits. Diazoxide, a K<sup>+</sup> channel opener, was tested for its ability to raise intraocular pressure in normal rabbits. Formulations were prepared in NaCl/borate buffer (0.8 mg NaCl, 1.0 mg boric acid, pH 7.2, water to 1 ml) and tested as follows: Seventy New Zealand white rabbits were divided into seven groups; 25 were treated with vehicle; 20 were treated with timolal; 10 were treated with glybenclamide; 5 with tolazamide; 10 with tolbutamide; 5 with chlorpropamide, and 5 with diazoxide. Each animal received 80  $\mu$ l of solution in two doses, 40  $\mu$ l each, at an interval of two minutes. Intraocular pressure was determined with a Tono-Pen before administration ("0" time), at one and two hours following administration. The results are set forth in Table 2.

TABLE 2

<u>Formulation</u> <sup>1</sup>		<u>Intraocular Pressure</u> <sup>2</sup>		
		<u>0 hr</u>	<u>1hr</u>	<u>2hr</u>
	Vehicle	100	100	100
5	1% Glybenclamide	100	92	97
	1% Tolazamide	100	86	93
	1% Tolbutamide	100	84	94
	1% Chlorpropamide	100	92	98
	1% Diazoxide	100	129	123

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1. Wt. percent of each compound.
2. Percent initial pressure.

The results presented in Table 2 clearly show that inhibitors of ATP-sensitive K<sup>+</sup> channels lower intraocular pressure. Of the four sulfonylureas, which are selective inhibitors of ATP-sensitive K<sup>+</sup> channels, tolbutamide and tolazamide appear to be more effective than glybenclamide or chlorpropamide. However, since these compounds are insoluble in aqueous solutions, the activity of these compounds in lowering intraocular pressure may be very different if they are administered in a vehicle in which they are soluble. Since the sulfonylureas which are selective inhibitors of the ATP-sensitive K<sup>+</sup> channels lower intraocular pressure, and since diazoxide, which is a K<sup>+</sup> channel opener, increases intraocular pressure, it appears that intraocular pressure is at least in part dependent on the ratio of intracellular to extracellular potassium.

Although the foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity of understanding, it will be obvious that certain changes and modifications may be practiced within the scope of the appended claims.

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WHAT IS CLAIMED IS:

1. A pharmaceutical composition for administration  
to the anterior chamber of the eye to lower intraocular  
5 pressure, said composition comprising an active compound  
selected from the group consisting of a quinine compound and an  
ATP-sensitive K<sup>+</sup> channel inhibiting compound acceptable carrier  
in an amount effective to lower intraocular pressure when  
administered to an eye having elevated intraocular pressure or  
10 low-tension glaucoma.
2. A pharmaceutical composition as in claim 1,  
wherein the active compound is present at concentration from  
0.1 to 5 percent by weight in the carrier.  
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3. A pharmaceutical composition as in claim 1, in a  
single dosage form having from 50 ug to 5 mg of the active  
compound.
- 20 4. A pharmaceutical composition as in claim 1,  
wherein the active compound is quinine or quinidine.
- 25 5. A pharmaceutical composition as in claim 1,  
wherein the active compound is an ATP-sensitive K<sup>+</sup> channel  
inhibiting compound selected from the group consisting of  
glybenclamide, glipizide, tolbutamide, and tolazamide,  
chlorpropamide or other sulfonylureas, and therapeutically  
equivalent salts or derivatives thereof.
- 30 6. A pharmaceutical composition as in claim 1,  
wherein the carrier is suitable for topical application to the  
eye.
- 35 7. A pharmaceutical composition as in claim 1,  
wherein the carrier is suitable for injection into the anterior  
chamber of the eye.

8. A pharmaceutical composition as in claim 1, wherein the quinine compound is present in an ocular insert.

5 9. A method for lowering intraocular pressure in an eye of a patient, said method comprising administering to the eye a quinine compound or ATP-sensitive  $K^+$  channel inhibiting compound present in a non-phosphate ophthalmically acceptable carrier in an amount effective to lower said intraocular pressure.

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10. A method as in claim 9, wherein the quinine compound is administered by topical application to the eye.

15 11. A method as in claim 9, wherein the quinine compound is administered by injection into the anterior chamber.

20 12. A method as in claim 9, wherein the quinine compound is administered using an ocular insert.

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13. A pharmaceutical composition as in claim 10, wherein the carrier is suitable for topical application to the eye.

25 14. A pharmaceutical composition as in claim 10, wherein the carrier is suitable for injection into the anterior chamber of the eye.

30 15. A pharmaceutical composition as in claim 10, wherein the quinine compound is present in an ocular insert.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 90/06278

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 31/445  
US CL :514/315, 316, 913

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
U.S. : 514/315, 316, 913

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
DIALOG

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US,A, 4,895,807 (CHERKSEY) 23 January 1990, entire document.	1-15

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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